



# Interleukin 10/ Interleukin-10R Mutations Causing Very Early Onset Inflammatory Bowel Disease

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## ABSTRACT

A unique disease entity called Very early onset inflammatory bowel disease [VEO-IBD] in which the affected patients show a complex genetic susceptibility. Various monogenic mutations which contribute to the pathogenesis of VEO-IBD have been attributed by gene sequencing techniques, including mutations in Interleukin 10 (IL-10) and Interleukin 10 receptor (IL-10R). The IL-10 pathway has an inhibitory effect on the release of several cytokines and hence, has an anti-inflammatory effect on the gastrointestinal tract. Among the reported patients with VEO-IBD in the world literature, mutations in the genes encoding for IL-10 and IL-10R have been detected. These patients present with symptoms of bloody diarrhea, significant weight loss, growth retardation and recurrent perianal abscesses, fistulas and fissures. Some patients may also have respiratory infections and folliculitis. As the therapeutic efficacy of immunosuppressive drugs is poor in these patients, it has been reported that allogeneic hematopoietic stem cell transplantation (HSCT) can improve the symptoms significantly. However, in order to verify the efficacy and safety of this treatment, and the long term prognosis of VEO-IBD patients with IL-10/IL-10R mutations, further study and exploration is yet required. In this article, we would conclude the importance for physicians to recognize the clinical phenotype of VEO-IBD and a mutational analysis of the IL-10/IL-10R can help in confirming the diagnosis and start early and effective treatment of this disease.

**Key Words:** Inflammatory Bowel Disease, Very early onset, Interleukin 10, Mutations

## INTRODUCTION

Inflammatory bowel disease (IBD) comprises of a group of chronic disorders of the gastrointestinal disorders which includes ulcerative colitis (UC) and Crohn's disease (CD). There have been a wide variety of factors responsible for the pathogenesis of these disorders, which are yet to be clarified. However, many studies have revealed that a variety of environmental factors trigger the chronic inflammation of the gut in genetically susceptible individuals which lead to IBD. IBD with a disease onset before 6 years of age has been termed very early onset IBD (VEO-IBD). Whereas on one hand, exogenous environmental factors are considered to play a major role in adolescent- and adult-onset IBD, in VEO-IBD, on the other hand, genetic susceptibility is considered to play a major role in its pathogenesis [1]. GWAS (Genome wide association studies) have found out as many

as 201 loci of gene mutations related to IBD [2]. Although GWAS can detect common genetic variants, it cannot identify low frequency monogenetic variants, which are more relevant to VEO-IBD[3]. These limitations of GWAS may be overcome by genetic linkage analysis and exome gene sequencing. By these new gene sequencing techniques, at-least 58 susceptible genes have been studied which have shown to be responsible for the pathogenesis of VEO-IBD [4]. Of all these susceptible genes, IL (Interleukin)-10 and IL-10R have been broadly studied and investigated. This article focusses on the review of the present literature on the mutations of IL-10 and IL-10R in the pathogenesis of VEO-IBD.

### Physiology of IL-10 in the Gut

A very important anti-inflammatory cytokine, IL-10, is secreted by monocytes, macrophages, dendritic cells, mast

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cells, epithelial cells, T and B lymphocytes. It inhibits Tumor necrosis factor-  $\alpha$  (TNF- $\alpha$ ) release, and hence, maintains the immune homeostasis in the gastrointestinal tract [5]. IL-10 binds to its receptor, IL-10R. IL-10R is a tetrameric complex which consists of two  $\alpha$  subunits of IL-10R1 that is encoded by IL-10RA; and two  $\beta$  subunits of IL-10R2 encoded by IL-10RB [6]. IL-10R1 only binds IL-10 but IL-10R1 binds to other cytokines as well (IL-22, IL-26, IL-28, IL-29) [7]. When IL-10 binds with its receptor, it leads to the activation of Janus kinase 1 (JAK1) and tyrosine kinase 2 (Tyk2), which in turn leads to the phosphorylation of STAT-3 (signal transducer and activator of transcription 3), activation of the downstream target genes, and finally, the anti-inflammatory effectors are expressed [8].

### IL-10 and IL-10R Mutations in VEO-IBD

The defects in the IL-10 and IL-10R signaling pathway can cause severe enterocolitis in humans [9], which has been observed in some cases of VEO-IBD. Mutations in IL-10 and IL-10R genes can lead to disturbance in the anti-inflammatory response. About 60 cases and more of VEO-IBD are documented in the present literature after the initial report by Glocker et al in 2009 [10]. Majority of the cases have been reported from Europe in which it was noticed that IL-10R mutations were more predominant than mutations in IL-10. 22 cases have been reported in East Asia, of which 21 cases showed IL-10RA mutation with only 1 case showing IL-10RB mutation. This is a contrast to the European cases in which IL-10RA and IL-10RB mutations were almost equal [10-27].

According to the available statistics, IBD accounts for approximately 20-25% of pediatric patients, with about 5% of patients being less than 10 years of age and 1% being less than 2 years old [1]. About 15% of the total pediatric IBD patients have been classified under VEO-IBD [27]. The Frequency of IL-10 and IL-10R mutations varied in the available cohort studies of VEO-IBD. Or example, in a report from the United Kingdom, 8.1% of IBD cases in patients below 2 years of age were confirmed to have mutations of IL-10 and IL-10R [28]. Similarly, a report from Germany showed that 24.2% of IBD cases less than 5 years old were verified to have IL-10 or IL-10R mutations [13]. A report from the United States showed about 4.8% of IBD patients with IL-10 mutations [24]. In Asian countries, it was noticed that VEO-IBD cases have higher rate of mutations of IL-10/IL-10R. A report from Korea showed 50% of children below 1 year of age with IL-10RA mutations [20]. In a report by Xiao et al [27] from China, it was verified that 38.5% of IBD cases were due to IL-10RA / IL-10RB mutations. This strikingly high frequency of mutations may be due to the small cohort study with only 13 VEO-IBD cases. However, from this currently available data from the case reports suggests that the frequency of gene mutations of IL-10/IL-10R is not low. Yet,

multi center studies are necessary to determine the role of genetic mutations of IL-10/IL-10R in the pathogenesis of VEO-IBD and to identify the definite clinical phenotype of the disease. This could be used as a screening tool to diagnose VEO-IBD patients with mutations in IL-10/IL-10R.

### Clinical Presentation in case of VEO-IBD associated with IL-10/IL-10R Mutations

The clinical features of VEO-IBD are different compared to that of adult-onset IBD. VEO-IBD shows more resistance to immunosuppressive therapy and has as severe clinical course. VEO-IBD associated with mutations of IL-10/IL-10R show an even more severe and complicated course of disease. These patients present with repeated episodes of bloody diarrhea, significant weight loss, growth retardation and recurrent perianal abscesses, fistulas and fissures [29]. Additionally, in patients with IL-10RB mutations which interrupts the binding between IL-10R1 and IL-22, results in the immune defects of the skin and lung epithelium due to IL-22 signal pathway abnormality, leads to folliculitis and refractory pneumonia [13,25].

Furthermore, this disease is also resistant to the various immunosuppressive drugs like corticosteroids, azathioprine, methotrexate and infliximab, either used as a single therapy or in combination. Treatment with these drugs results in either no improvement or only a mild improvement of the clinical features. Due to poor efficacy of treatment and drug resistance, some patients have undergone bowel resection and ileostomy or colostomy [22]. As a matter of fact that IL-10 has a predominant action on the immune and hematopoietic cells, an attempt has been made to use Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) as a curative therapy for patients of VEO-IBD with mutations of IL-10/IL-10R [10,13,17,19,23,25,30]. Though the initial results have supported the curative role of HSCT in VEO-IBD patients with IL-10/IL-10R mutations, yet its experience is limited because it has been used only in a few number of patients with a short follow-up period. HSCT yet proves a promising therapeutic modality but more studies are necessary to confirm its efficacy and long term safety in VEO-IBD patients with mutations of IL-10/IL-10R.

### CONCLUSION

Though VEO-IBD was considered a rare disease, it is noted to be more frequent and is considered as an emerging disease. This makes it important for the clinicians to detect the phenotype of gene mutations of IL-10/IL-10R causing VEO-IBD by gene analysis for a prompt diagnosis and effective treatment of these patients. Moreover, in patients who are resistant to the standard available therapy with immunosuppressive drugs, an alternative treatment option is the use of

allogenic HSCT which may prove efficacious in a setting of a clinical trial.

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## REFERENCES

- Snapper SB. Very-Early-Onset Inflammatory Bowel Disease. *Gastroenterol Hepatol* (N Y) 2015;11(8):554–556.
- Loddo I, Romano C. Inflammatory Bowel Disease: Genetics, Epigenetics, and Pathogenesis. *Front Immunol*. 2015;6:551.
- Uhlig HH. Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. *Gut*. 2013;62(12):1795–1805.
- Bianco AM, Girardelli M, Tommasini A. Genetics of inflammatory bowel disease from multifactorial to monogenic forms. *World J Gastroenterol*. 2015;21(43):12296–12310.
- Hutchins AP, Diez D, Miranda-Saavedra D. The IL-10/STAT3-mediated anti-inflammatory response: recent developments and future challenge. *Brifunct Genomics*. 2013;12:489–498.
- Ding Y, Qin L, Zamarin D, Kotenko SV, Pestka S, Moore KW, Bromberg JS. Differential IL-10R1 expression plays a critical role in IL-10-mediated immune regulation. *J Immunol*. 2001;167(12):6884–6892.
- Commings S, Steinke JW, Borish L. The extended IL-10 superfamily: IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29. *J Allergy Clin Immunol*. 2008;121(5):1108–1111.
- Murray PJ. The primary mechanism of the IL-10-regulated anti-inflammatory response is to selectively inhibit transcription. *Proc Natl Acad Sci U S A*. 2005;102(24):8686–8691.
- Engelhardt KR, Grimbacher B. IL-10 in humans: lessons from the gut, IL-10/IL-10 receptor deficiencies, and IL-10 polymorphisms. *Curr Top Microbiol Immunol*. 2014; 380: 1–18.
- Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schaffer AA, Noyan F, Perro M et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med*. 2009;361(21):2033–2045.
- Begue B, Verdier J, Rieux-Laucat F, Goulet O, Morali A, Canioni D, Hugot JP et al. Defective IL10 signaling defining a subgroup of patients with inflammatory bowel disease. *Am J Gastroenterol*. 2011;106(8):1544–1555.
- Mao H, Yang W, Lee PP, Ho MH, Yang J, Zeng S, Chong CY et al. Exome sequencing identifies novel compound heterozygous mutations of IL-10 receptor 1 in neonatal-onset Crohn's disease. *Genes Immun*. 2012;13(5):437–442.
- Kotlarz D, Beier R, Murugan D, Diestelhorst J, Jensen O, Boztug K, Pfeifer D et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. *Gastroenterology*. 2012;143(2):347–355.
- Shim JO, Hwang S, Yang HR, Moon JS, Chang JY, Ko JS, Park SS et al. Interleukin-10 receptor mutations in children with neonatal-onset Crohn's disease and intractable ulcerating enterocolitis. *Eur J Gastroenterol Hepatol*. 2013;25(10):1235–1240.
- Moran CJ, Walters TD, Guo CH, Kugathasan S, Klein C, Turner D, Wolters VM et al. IL-10R polymorphisms are associated with very-early-onset ulcerative colitis. *Inflamm Bowel Dis*. 2013;19(1):115–123.
- Neven B, Mameessier E, Bruneau J, Kaltenbach S, Kotlarz D, Suarez F, Masliah-Planchon J et al. A Mendelian predisposition to B-cell lymphoma caused by IL-10R deficiency. *Blood*. 2013;122(23):3713–3722.
- Pigneur B, Escher J, Elawad M, Lima R, Buderus S, Kierkus J, Guariso G et al. Phenotypic characterization of very early-onset IBD due to mutations in the IL10, IL10 receptor alpha or beta gene: a survey of the Genius Working Group. *Inflamm Bowel Dis*. 2013;19(13):2820–2828.
- Galatola M, Miele E, Strisciuglio C, Paparo L, Rega D, Delrio P, Duraturo F et al. Synergistic effect of interleukin-10-receptor variants in a case of early-onset ulcerative colitis. *World J Gastroenterol*. 2013;19(46):8659–8670.
- Murugan D, Albert MH, Langemeier J, Bohné J, Puchalka J, Jarvinen PM, Hauck F et al. Very early onset inflammatory bowel disease associated with aberrant trafficking of IL-10R1 and cure by T cell replete haploidentical bone marrow transplantation. *J Clin Immunol*. 2014;34(3):331–339.
- Shim JO, Seo JK. Very early-onset inflammatory bowel disease (IBD) in infancy is a different disease entity from adult-onset IBD; one form of interleukin-10 receptor mutations. *J Hum Genet*. 2014;59(6):337–341.
- Lee CH, Hsu P, Nanan B, Nanan R, Wong M, Gaskin KJ, Leong RW et al. Novel de novo mutations of the interleukin-10 receptor gene lead to infantile onset inflammatory bowel disease. *J Crohns Colitis*. 2014;8(11):1551–1556.
- Beser OF, Conde CD, Serwas NK, Cokugras FC, Kutlu T, Boztug K, Erkan T. Clinical features of interleukin 10 receptor gene mutations in children with very early-onset inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2015;60(3):332–338.
- Lu D, Xu Y, Chen Y, Zeng P, Chen H, Zeng H. [Interleukin-10 receptor mutations in children with neonatal onset inflammatory bowel disease: genetic diagnosis and pathogenesis] *Zhonghua Er Ke Za Zhi*. 2015;53(5):348–354.
- Kelsen JR, Dawany N, Moran CJ, Petersen BS, Sarmady M, Sasson A, Pauly-Hubbard H et al. Exome sequencing analysis reveals variants in primary immunodeficiency genes in patients with very early onset inflammatory bowel disease. *Gastroenterology*. 2015;149(6):1415–1424.
- Yanagi T, Mizuochi T, Takaki Y, Eda K, Mitsuyama K, Ishimura M, Takada H et al. Novel exonic mutation inducing aberrant splicing in the IL10RA gene and resulting in infantile-onset inflammatory bowel disease: a case report. *BMC Gastroenterol*. 2016;16:10.
- Oh SH, Baek J, Liany H, Foo JN, Kim KM, Yang SC, Liu J et al. A Synonymous Variant in IL10RA Affects RNA Splicing in Paediatric Patients with Refractory Inflammatory Bowel Disease. *J Crohns Colitis*. 2016;10(11):1366–1371.
- Xiao Y, Wang XQ, Yu Y, Guo Y, Xu X, Gong L, Zhou T et al. Comprehensive mutation screening for 10 genes in Chinese patients suffering very early onset inflammatory bowel disease. *World J Gastroenterol*. 2016;22(24):5578–5588.
- Kammermeier J, Dziubak R, Pescarin M, Drury S, Godwin H, Reeve K, Chadokufa S et al. Phenotypic and Genotypic Charac-

- terisation of Inflammatory Bowel Disease Presenting Before the Age of 2 years. *J Crohns Colitis*. 2017;11(1):60–69
29. Engelhardt KR, Shah N, Faizura-Yeop I, KocacikUygun DF, Frede N, Muise AM, Shteyer E. et al. Clinical outcome in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. *J Allergy Clin Immunol*. 2013;131(3):825–830.
30. Gassas A, Courtney S, Armstrong C, Kapllani E, Muise AM, Schechter T. Unrelated donor hematopoietic stem cell transplantation for infantile enteropathy due to IL-10/IL-10 receptor defect. *Pediatr Transplant*. 2015;19(4):E101–103.